ANTIBIOTIC SUSCEPTIBILITY PATTERNS OF DIFFERENT BACTERIA ISOLATED FROM PATIENTS WITH VENTILATOR ASSOCIATED PNEUMONIA (VAP)

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هدف الدراسة : أنمالى الحساسية الدوائية للمضادات الحيوية تجاه الجراثيم المختلفة المعزولة من المرضى المصابين بذات لرئة الموضوعين على أجهزة التنفس الصناعي .
يعد الالتهاب الرئوي المصاحب لأجهزة التنفس الاصطناعية من المضاعفات المحتملة لهذه الأجهزة ومن الأسباب المؤدية إلى الوفاة في هؤلاء المرضى.
نتائج الدارسة : لقد أثبتت الدراسة أن الالتهاب الرئوي المصاحب لأجهزة التنفس الاصطناعية قد يحدث بسبب استنشاق الإفرازات الفمية البلعومية أو استنشاق أبخرة أنابيب الأجهزة أو استنشاق العصارة المعدية التي قد تحتوي على أحياء دقيقة مرضية . كان الهدف من هذه الدراسة هو عزل وتحديد البكتريا المسببة للالتهاب الرئوي المصاحب لأجهزة التنفس الاصطناعية وقياس حساسيتها للمضادات الحيوية . تم إجراء الدراسة على 95 مريضاً ممن تم تشخيصهم مرضى بالالتهاب الرئوي المصاحب لأجهزة التنفس الاصطناعية. وقد أجريت زراعة بكتيرية كمية للإفرازات الموجودة بالقصبة الهوائية باستخدام حد أدنى للزراعة البكتيرية هو مليون مستعمرة بكترية لكل ملي من الإفرازات .
لقد أظهر الفحص المجهري أن البكتريا العصوية السالبة لصبغة جرام هي أكثر نوع بكتيري مسبب للالتهاب الرئوي من الكلبسيلا في 9. 30% كانت مزرعة الدم إيجابية في 9ز 25% من المصابين بالالتهاب الرئوي المصاحب لأجهزة التنفس الاصطناعية وكانت الكلبسيلا موجودة في 3. 33% من مزارع الدم الاصطناعية هو من أكثر حالات العدوي داخل المستشفيات . كما أنه يمكن إجراء امتصاص إفرازات من داخل الأنابيب بالقصبة الهوائية وإجراء اختبار الحساسية بها . وأن البكتريا العصوية السالبة لصبغة جرام هي أكثر نوع بكتيري مسبب للالتهاب الرئوي المصاحب لأجهزة التنفس الاصطناعية .

الكلمات المرجعية : الالتهاب الرئوي ، أجهزة التنفس الاصطناعية ، المضادات الحيوية .

Objective: *Ventilator associated pneumonia (VAP) is a frequent complication of mechanical ventilation (MV) and it is a leading cause of death in MV patients. The development of VAP has been demonstrated as being due to aspiration of oropharyngeal secretion, ventilator tubing condensate, or gastric contents that are colonized with pathogenic microorganisms. The aim of the present study is to isolate and identify bacteria that cause VAP and to study antibiotic susceptibility.*
Material and Methods*: This study was carried out on 95 patients who fulfilled the diagnostic criteria for VAP. Quantitative cultures of endotracheal aspirates (EA) using a cut-off point of 10^6 cfu/ml was done.*
Results*: The microbiological results revealed that gram negative bacilli were the most common bacterial agents responsible for VAP and accounted for 78.8% of all the causative agents. The most common isolated organisms were Klebsiella pnemouniae (30.9 %) followed by Pseudomonas aeruginosa (22.5%), Staphylococcus aureus (21.2%), Eschericia coli (12.8 %), Proteus spp. (9.8%), and Citrobacter spp. (2.8%). Blood cultures were positive in 25.9% of patients with Klebsiella pnemouniae in about 33.3%.*

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***Conclusion**: From this study, it can be concluded that VAP is an important nosocomial infection. EA is a simple procedure to obtain respiratory samples and perform sensitivity testing in patients with VAP. Also, the commonest cause of VAP is gram negative bacilli.*

***Key Words**: Pneumonia, mechanical ventilation, antibiotics.*

INTRODUCTION

Ventilator associated pneumonia is a nosocomial pneumonia (not present at the time of air way intubation) developing in mechanically ventilated patients.[1] Mechanical ventilation is defined as any period of respiratory support with tracheal intubation.[2]

The development of VAP has been demonstrated as being primarily due to the aspiration of oropharyngeal secretion, ventilator tubing condensate, and/or gastric contents that are colonized with pathogenic microorganisms.[3,4] The diagnosis of VAP is based upon a combination of clinical, bacteriological, and radiological criteria.[5]

Diagnosis of VAP is a difficult problem and presents a major diagnostic challenge, because the reliability of the criteria commonly used to diagnose pneumonia is uncertain in MV patients.[6] In MV patients, the clinical and microbiologic distinction between colonization and infection is often extremely difficult.[7] There is considerable controversy on the sampling techniques used in diagnosing bacterial pneumonia and in identifying the causal pathogen. Quantitative culture of samples obtained by bronchoscopic techniques, such as protected specimen brush (PSB) and bronchoalveolar lavage (BAL) have shown satisfactory diagnostic accuracy for the diagnosis of VAP.[5] These methods are invasive, expensive and not exempt from complications requiring bronchoscopic procedure, which is a technique not always available 24 hours a day in the intensive care setting.[7]

Quantitative culture of endotracheal aspirate using a cut-off point 10^5 and 10^6 cfu/ml may play a practical role in diagnosing VAP, as good correlations between the results of quantitative cultures of PSB or BAL and those of quantitative cultures EA have been reported by many workers.[8,9] The main objective of the present study was the isolation and identification of bacteria causing VAP, testing their antibiotic susceptibility in order to make recommendations to minimize the risk of occurrence of VAP in hospitals.

MATERIAL AND METHODS

This study was carried out on 95 patients; 68 males and 27 females, selected from those attending medical and surgical ICUs from some governmental and private hospitals in the Dammam and Al-Khobar areas, Saudi Arabia. There was an age range of one year to 85 years. The inclusion criteria were that they had been mechanically ventilated for more than 48 hours and on clinical grounds were suspected to have VAP.[10] VAP was suspected when there was a new, persistent, or progressive lung infiltrate in the chest radiograph and at least two of the following criteria: fever 38^0C, leucocytosis 10,000 or leucopenia 40,000 and purulent tracheal aspirates.[11] Samples for diagnosis of VAP were collected by endotracheal aspirate *(*EA*)*.[7]

Direct Gram stained films were examined for the presence of microorganisms, epithelial cells, neutrophils and macrophages.[12] Serial dilutions (1:10, 1:100 and 1:1000) were prepared from each EA sample and were inoculated into the following media: 5% sheep blood, chocolate and Mac Conkey agars for aerobic culture and anaerobic cultures. All organisms isolated were identified by standard laboratory methods.[13,14] Results were expressed as colony forming unit/ml [CFU=Number of colonies x Dilution factor x Inoculation factor].[7] Five ml of blood samples were obtained for blood culture. The criteria of positive count (10 c f u /ml).[8,9]

Antibiotic susceptibility testing was performed on Muller-Hinton agar using Kirby-Bauer disc diffusion method.[15] The antibiotic discs were selected according to the protocol of the laboratory of MDICU, as recommended by the National Committee for Clinical Laboratory Standards (NCCLS).

RESULTS

This study was done on 95 patients (68 males and 27 females, with average age of one year to 85 years with clinically suspected VAP. They included neurological disease (11 cases), post surgical 23, (neurosurgery 10, orthopedic surgery 7, abdominal surgery 6), pancreatitis 4, burns 3, eclampsia 4, liver failure 5, heart failure 4 and cancer 3 with a predominance of trauma 38, (head 22 and multiple 16),.

1. Results of direct smear

The direct Gram stained smears of EA results showed a count of more than 25 neutrophils in 66 (69.4%) samples out of 95 collected and positivity for gram negative bacilli and gram cocci only 35 (36.8%) of samples.

2. Results of quantitative culture of EA

Fifty-eight (61.1%) of the available EA specimens grew a total of 71 bacterial isolates. Quantitative cultures reached the 10^6cfu\ml (threshold of positivity for respiratory secretions) in 58 (61.1%) patients (positive cases), and were below this threshold in 37 (26.27) patients (negative cases).

The most common organisms isolated were *Klebsiella pnemouniae* 22 (30.9 %) followed by *Pseudomonas aeruginosa 16* (22.5%), *Staphylococcus aureus 15* (21.2%), *E. coli 9* (12.8 %), *Proteus* spp.7 (9.8%), and *Citrobacter* spp.2 (2.8%). Gram negative bacilli accounted for 56 (78.8%) of the total isolates. The cultures were monomicrobial in 45 cases, 55 (77.6%) yielded 45 isolates and were polymicrobial in 13 cases yielding 26 isolates, with a total of 71 isolates.

3. The correlation between bacteremia and *VAP*

Blood culture showed that 15 (25.9%) out of 58 patients with VAP had positive blood cultures. 5 (33.3%) out of 15 cases of the positive blood cultures were positive to the same organism isolated from respiratory samples. Isolates from blood cultures of patients with VAP were: *Staphylococcus aureus* in 10 (66.7%)cases, *Pseudomonas aeruginosa* in 2 (13.3%)cases, *E. coli* in 2 (13.3%)cases, and *Proteus* spp. in only 1 (6.7%)case. Statistically there was significant correlation between bacteraemia and VAP ($p<0.05$).

4. Antimicrobial Susceptibility Patterns

Susceptibility of various antibiotics tested against the isolates from VAP are given in Table 1. It shows that *Klebsiella pneumoniae* 22 (100%) were sensitive to aztereonam, 20 (91%) to imipinem, 19 (86.3%) to cefuroxime, 18 (82%)to ciprofloxacin, 11 (50%) to amikacin, 10 (45.5%) to trimethoprim, 9 (40.9%) to cefotaxime, 8 (36.3%) to cefoxitin and gentamicin. Only 2 (9%) were intermediately sensitive to sulbactam-ampicillin, while 22 (100%) were resistant to ampicillin and amoxicillin-clavulinic acid.

Pseudomonas aeruginosa isolates sensitive to imipinem were 16 (100%), aztereonam 10 (62.5%), ciprofloxacin 9 (56.3%), ceftazidime and trimethoprim 6 (37.5%), sulbactam-ampicillin 5 (31.2%), gentamicin and amoxicillin-clavulinic acid 4 (25%), cefotaxime and amikacin 3 (18.8%), intermediately sensitive to piperacillin 2 (15.5%) and 14 (87.5%) resistant to carpenicillin.

Staphylococcus aureus isolate*s* sensitive to rifampin and vancomycin were 15 (100%), 11 (73.3%) to sulbactam-ampicillin, 10 (66.7%) to ciprofloxacin, 9 (60%) to imipinem and amoxicillin-clavulinic acid, 8 (53.3%)to tetracycline, 7 (46.7%) to cefuroxime and trimethoprim, 6 (40%) to ampicillin, while 2 (13.3%) were resistant to gentamicin; MRSA represented 40%.

Escherichia coli sensitive to aztereonam and imipinem were 9 (100%), 6 (75%) to ciprofloxacin, 4 (44.4%) to sulbactam-ampicillin and amoxicillin-clavulinic acid 2 (25%) to cefuroxime. Two (22.2%) to amikacin and gentamicin, one (11.1%) to trimethoprim-sulphamethoxazole and cefotaxime, and 9 (100%) resistant to both ampicillin and cefoxitin.

All *Proteus* spp. were sensitive to aztereonam, imipinem, and cefuroxime, while 5 (71.4%) were sensitive to amikacin, cefoxitin, and ciprofloxacin, 3 (42.8%) to ciprofloxacin, amoxicillin-clavulinic acid, and trimethoprim, 2 (28.6%) to ampicillin and sulbactam-ampicillin, while 6 (85.6%) were resistant to gentamicin and cefotaxime.

All the *Citrobacter* spp. were sensitive to aztereonam, cefotaxime, imipinem, ciprofloxacin, ceforuxime sulbactam-ampicillin amoxicillin-clavulinic acid and ampicillin and one (50%)

***Table 1**: Antimicrobial susceptibility patterns of bacteria isolated as causative agents of VAP*

Antibiotic	Klebsiella pneumoniae	Pseudomonas areuginosa	Proteus spp.	Escherichia coli	Citrobacter spp.	Staphylococcus aureus
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Penicillin	-	-	-	-	-	4 (26.7)
Ampicillin	-	-	2 (28.6)	-	1 (50.0)	6 (40.0)
Methicillin	-	-	-	-	-	9 (60.0)
Amoxicillin-clavulinic acid	-	4 (25.0)	3 (42.8)	3 (25.0)	2 (100)	9 (60.0)
Sulbactam-ampicillin	2 (9.0)	5 (31.2)	2 (28.6)	4 (44.4)	2 (100)	11 (73.3)
Carbenicillin	-	2 (12.5)	-	-	-	-
Cefoxitin	8 (36.3)	-	5 (71.4)	-	-	-
Ceftazidime	-	6 (37.5)	-	-	2 (100)	-
Cefotaxime	9 (40.9)	3 (18.8)	1 (14.4)	1 (11.1)	2 (100)	-
Cefuroxime	19 (86.3)	-	7 (100)	3 (25.0)	2 (100)	7 (46.7)
Azteronam	22 (100)	10 (62.5)	7 (100)	9 (100)	2 (100)	-
Imipinem	20 (91.0)	16 (100)	7 (100)	9 (100)	2 (100)	9 (60.0)
Gentamicin	8 (36.3)	4 (25.0)	1 (14.4)	2 (22.2)	1 (50.0)	3 (20.0)
Amikacin	11 (50.0)	3 (18.8)	5 (71.4)	2 (22.2)	-	-
Ciprofloxacin	18 (82.0)	9 (56.3)	3 (42.8)	6 (75.0)	2 (100)	10 (66.7)
Trimethoprim	10 (45.5)	6 (37.5)	3 (42.8)	1 (11.1)	1 (50.0)	7 (46.7)
Tetracycline	-	-	-	-	-	7 (46.7)
Rifampicin	-	-	-	-	-	15 (100)
Vancomycin	-	-	-	-	-	15 (100)
Total number of bacterial strains of each species	**22**	**16**	**7**	**9**	**2**	**15**

was sensitive to gentamicin, amikacin; intermediate sensitive to trimethoprim and cefoxitin.

DISCUSSION

Ventilator associated pneumonia (VAP) is a major problem and is the most frequently encountered hospital acquired infection in the ICU,[15] and related to a high mortality rate. This complication of mechanical ventilation (MV) therefore, requires prompt diagnosis and adequate antibiotic treatment. The detection of the causative organism is imperative for the selection of an appropriate therapy as there is strong evidence of adverse outcome of inadequate empirical treatment.[16]

The aim of this work was to determine the incidence and the causative organisms of VAP. From May 2001 till June 2002, 95 patients suspected to have VAP were studied. This decision depended on the presence of new and progressive pulmonary radiographic infiltrates, fever and leukocytosis in mechanically ventilated (MV) patients for more than 48 hours.

By direct microscopic examination, it was found that 66 out of 95 endotracheal aspirate samples from clinically suspected cases of VAP, were purulent as they showed more than 25 neutrophils per high power field. This is similar to the results of Pugin et al[7] who found a significant increase in total neutrophil count in the respiratory samples in patients with VAP. The morphology of microorganisms was positive in only 35 (36.8 %) samples. However, Blot et al[18] reported that gram stain examination may contribute to the early diagnosis of nosocomial pneumonia in about two thirds of MV patients and may guide to empiric therapy.

Quantitative cultures of the homogenized EA and the presence of bacteraemia by blood culture were used. Several studies have suggested that the use of quantitative cultures of EA, a noninvasive & easily repeatable procedure, may have a similar diagnostic value compared with such invasive techniques as PSB and BAL which are expensive, time consuming, and require bronchoscopic procedure, a technique not always available throughout the day in the intensive care setting.[19,20] Therefore, quantitative culture of EA can be an alternative to a more sophisticated testing in diagnosing VAP.[21]

In this study, Gram negative bacilli were the most common bacterial agents responsible for VAP and accounted for 78.8% of the causative agents. Similar results were shown by Fugon et al[6] who reported an incidence of 75% of gram negative bacilli and Simsek et al who reported an incidence of 72% of gram negative bacilli. [15]

The incidence of various isolates from patients with VAP is comparable to some studies but also different from others.[22,23] It was found that 22%of our cultures were polymicrobial; while variable results have been reported in other studies ranging from 13% to 87%.[24-26] Although in this study, all samples were incubated anaerobically, no anaerobes were isolated.

The variations in the types and incidence of the isolated organisms found can be attributed to the variation in the patient populations studied, the method used to obtain and analyze specimens and the definitions used for VAP,[27] local specificities, comorbid conditions, length of hospital stay, intubation, and use of antimicrobials.[28] Local specificities may be the result of the differences between our patient population and those of other community hospitals. Besides, pathogens associated with VAP have been shown to vary among different hospitals. This suggests that hospitals need to locally identify the bacterial pathogens associated with hospital acquired infections in order to optimize antibiotic utilization.[29-33]

CONCLUSION

From this study, we can conclude that VAP is an important nosocomial infection, the commonest cause of which is gram negative bacilli. EA is a simple procedure for obtaining respiratory samples and performing sensitivity testing in patients with VAP.

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ERRATUM

The August issue (Vol.12, No.2) contain an error. The original article entitled, "Giant Juvenile Fibroadenoma: Experience from a University Hospital" of Maha S.A. AbdelHadi was included under "Case Report". It is an original article and has to be read under "Original Articles".